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Effects of Oral, Subchronic Cadmium Administration on Fertility, Prenatal and Postnatal Progeny Development in Rats

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Abstract. Cadmium chloride was administered by gavage to female rats 5 days a week for 5 weeks, then during mating and gestation periods at doses of 0.04, 0.4, and 4 mg Cd/kg/day. Treatment with cadmium neither affected the survival and fertility of females, nor produced overt fetotoxic effects. Fetal cadmium concentration was not related to the level of exposure. Litter size, body weight gain and viability of offspring during 2 months after parturition were similar in all groups. The exploratory locomotor activity of 2-month-old males and females born to rats given 0.4 and 4 mg Cd/kg/day was significantly reduced. The progeny of cadmium-treated females showed decreased performance in the rotarod test. In general, the degree of behavioral impairment was dose-related.

Key words: Cadmium – Prenatal toxicity – Behavioral deficit – Rat

Introduction

Cadmium, an environmental contaminant, poses a health risk to directly exposed animals and their progeny. Dietary cadmium exposure of mice and rats prior to and/or during pregnancy results in anemia and reduced body weight of pups at birth (Webster 1978; Petering et al. 1979), and distinct changes in trace metal metabolism in pups (Pond and Walker 1975; Petering et al. 1979). Oral exposure of pregnant rats to low levels of cadmium does not affect fetal growth and morphology (Sutou et al. 1980; Barański et al. 1982), but it causes persistent reduction in spontaneous locomotor activity in the offspring and little or no change in their body weights, dependent on level of maternal exposure (Cooper et al. 1978; Choudhury et al. 1978).

The effect of prenatal cadmium exposure is of particular interest, since this element is widely distributed in the environment. The daily human intake of

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cadmium with food amounts to 10–120 μg (CEC 1978) and it may reach several hundred micrograms in polluted areas (Piscator 1979). The estimated amount of cadmium deposited daily in the lungs due to environmental exposure varies from 0.0005 to 28 μg depending on air concentration and cigarette smoking habit (CEC 1978).

This study was aimed to assess the influence of low level oral cadmium exposure of female rats on fetal development and growth, viability and behavior of offspring.

Materials and Methods

Three-month-old female Wistar rats with mean body weight of 192 ± 10 g were obtained from our institute breeding celony. Before fertilization, the animals were housed in plastic cages, three to four per cage. During gestation and lactation periods the females were kept individually in similar plastic cages. They were freely fed on a commercial, pelleted chow and tap water. The females were distributed into one control and three treatment groups. The treatment groups received 5 days a week, by gavage, 0.04, 0.4, and 4.0 mg Cd/kg/day as an aqueous solution of $CdCl_2$. The control group was given, by gavage, an equivalent volume of water. After 5 weeks of treatment all females were mated with untreated 4-month-old male rats for a maximum of 3 weeks. The day of detection of spermatoza in vaginal smears was assumed to indicate day 1 of gestation. Administration of cadmium was continued throughout the mating period and gestation. Each group was further divided into two subgroups.

The females from the first subgroups, on day 21 of gestation, were sacrificed and subjected to autopsy. The assessment of fetotoxic and structural teratogenic effects and the determination of cadmium concentration in the fetuses were performed using methods presented previously (Barański 1982).

Female rats from the other subgroups were allowed to deliver and feed their progeny. The number of living and dead pups and the body weight of offspring within each litter were noted during 2 months after parturition. The indices of viability, lactation, and mortality were determined. At the age of 2 months, spontaneous locomotor activity and locomotor coordination of movements in the rotarod test were assessed in randomly chosen male and female pups. The locomotor activity of animals was determined in automated activity cages (Activity Meter type AM-1, IBD PAN, Warsaw, Poland). The rats were placed individually in the instruments and their exploratory locomotor activity was measured for 5 min during 5 consecutive days. In the rotarod test the animal was placed on a wooden rod, 8 cm in diameter, suspended horizontally 30 cm above the floor and rotated at 6 rpm. The length of stay on the rod served as an index of locomotor coordination. Three trials separated by 20-min rest periods were conducted daily over 6 days.

For statistical evaluation of results one-way analysis of variance and Dunnett's test (Dunnett 1955) or Kruskal-Wallis analysis of variance followed by non-parametric tests (Kruskal et al. 1952; Wilcoxon 1945; Wilcoxon and Wilcox 1964) were used where appropriate. Frequency data were analysed with Fisher's exact probability test (Siegel 1956). The effect of cadmium on behavioral performance and body weight gain of offspring was evaluated with two-way analysis of variance and Scheffe's test for multiple comparison (Scheffe 1959; Winer 1962).

Results

Treatment with cadmium did not affect the survival of female rats, although some deaths were noted in the highest dose group. The percentage of inseminated and pregnant females was similar in each treatment group. The average numbers of total implantations, corpora lutea, live fetuses and

resorptions were not different in cadmium-treated and control groups. Fetal length and body weight, fetal cadmium concentration, and placental weight remained similar in all groups. External and visceral examinations of fetuses did not reveal gross malformation in any group; however, the percentage of litters which had fetuses with subcutaneous edema in the group receiving 0.4 mg Cd/kg/day was significantly increased (47% as compared with 12% in the control

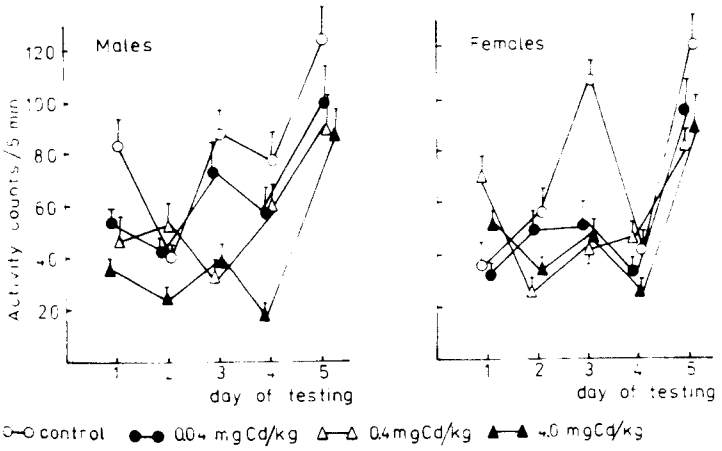

Fig. 1. Exploratory locomotor activity of 2-month-old male and female rats born to female rats given orally before and during gestation cadmium chloride at a daily dose of 0.04, 0.4, and 4.0 mg Cd/kg. The values presented represent means ± SE with eight animals in each group. Two-way analysis of variance and Scheffe's test indicated the following significant ($p < 0.05$) differences: Males: control vs 0.4 Cd, control vs 4.0 Cd, 0.04 Cd vs 4.0 Cd. Females: control vs 0.04 Cd, control vs 0.4 Cd, control vs 4.0 Cd

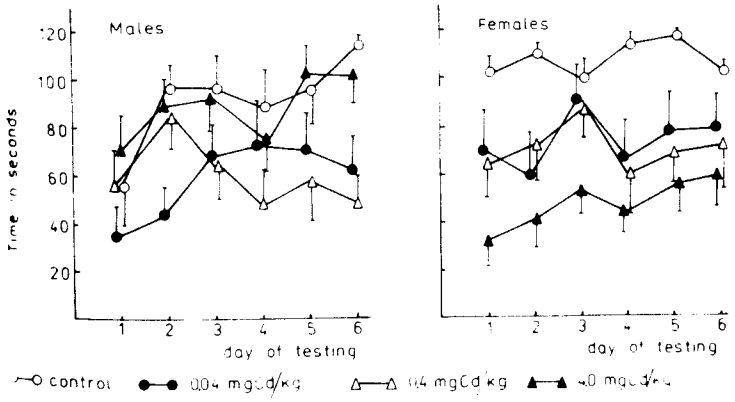

Fig. 2. Length of stay on a rod rotating at 6 rpm by 2-month-old males and females born to female rats given orally before and during gestation cadmium chloride at daily doses of 0.04, 0.4, and 4.0 mg Cd/kg. The values presented represent means ± SE with eight animals in each group. Two-way analysis of variance and Scheffe's or Dunnett's tests indicate the following significant ($p < 0.05$) differences: Males: control vs 0.04 Cd, control vs 0.4 Cd. Females: control vs 0.4 Cd, control vs 4.0 Cd

group; $p < 0.05$). The numbers of litters and fetuses with delayed ossification were not influenced by cadmium treatment. The litter size and the viability, lactation or mortality indices, as well as the body weight gain of offspring during the first 2 months of life showed no significant differences between control and treatment groups. The oral administration of cadmium to female rats prior to and during gestation did, however, affect the exploratory locomotor activity and performance of their 2-month-old progeny in the rotarod test. The locomotor activity of female offspring of all cadmium-treated rats was significantly decreased in comparison with controls (Fig. 1). The male offspring of females given 0.4 and 4 mg Cd/kg/day exhibited lower locomotor activity than controls, and the males born to females receiving 4 mg Cd/kg/day had lower activity than males born to females given 0.04 mg Cd/kg/day (Fig. 1).

The length of stay on the rotating rod by female offspring of rats receiving 0.4 and 4 mg Cd/kg/day orally and by males born to rats given 0.04 and 0.4 mg Cd/kg/day was significantly shorter than that of the respective controls (Fig. 2). The decreased performance in behavioral tests of progeny of cadmium-treated female rats was, except for locomotor coordination of males, related to the level of exposure.

Discussion

Cadmium at low levels of oral exposure, although still higher than those encountered in the contaminated environment, neither reduces the fertility of female rats, nor produces embryotoxicity or fetal lethality. This finding agrees with the data of Sutou et al. (1980) who did not observe reduced fertility of female rats given cadmium orally unless the exposure level was high enough to induce anemia and damage to internal organs.

Behavioral impairment of 2-month-old progeny was observed, although there were no prenatal developmental abnormalities and there was no effect on postnatal growth of neonates. Our data confirm and extend the finding of Choudhury et al. (1978) and Cooper et al. (1978) who observed a reduction in spontaneous locomotor activity of rats as a result of maternal exposure to cadmium in drinking water at a concentration of 4.3–17.2 μg/ml.

With the presented data, it is impossible to determine whether the critical period of cadmium-induced CNS dysfunction is limited to prenatal and/or neonatal developmental stages. No increase in fetal cadmium concentration was found in any of the cadmium-treated groups; an observation in agreement with the data of other studies (Choudhury et al. 1978; Petering et al. 1979; Barański et al. 1982). Although it has been shown that radioactive cadmium injected subcutaneously into pregnant rats is detectable in liver, gastrointestinal tract, and brain of newborns (Lucis et al. 1972), Rohrer et al. (1979) did not detect histopathological alterations in fetal rat brain, when pregnant mothers received single intraperitoneal injections of 1.0 or 2.0 mg Cd/kg. Cadmium is taken up in the mammary gland and it is excreted throughout the lactation period in small amounts via milk (Miller et al. 1967; Lucis et al. 1972). Shortly after birth, the brain is very susceptible to toxic agents. In the rat and rabbit cadmium damages

the central nervous system only when administered during the first days of life (Gabbiani et al. 1967).

Independently of the possible direct action of cadmium on the brain of progeny, the behavioral changes may be associated with the reduced content of iron, zinc, and copper found in fetuses and neonates of rats exposed to cadmium (Pond and Walker 1975; Cooper et al. 1978; Choudhury et al. 1978; Petering et al. 1979; Samarawickrama and Webb 1979; Webb and Samarawickrama 1981).

It cannot be stated whether cadmium-induced CNS dysfunction is a long-lasting phenomenon, but it has to be pointed out that the relatively low oral cadmium exposure of female rats, only moderately higher than that of humans in heavily polluted areas, is sufficient to cause CNS damage in their offspring.

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